# Natural history of hepatocellular carcinoma

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*Hepatocellular carcinoma (HCC) is a slowly growing tumor, whose natural history is not completely known. Since the hepatocarcinogenetic process may evolve for years in a stepwise fashion from premalignant to overt HCC, detection of early, better treatable tumors is made possible by surveillance of patients at risk. A 6-month interval surveillance with ultrasound is considered cost-effective, generally leading to the identification of a single < 3 cm tumor in 50-70% of the patients at risk. For greater than 2 cm tumors, demonstration of arterial hypervascularization of the node by sonovue US, triphasic spiral CT or MRI is diagnostic for HCC. The diagnosis of a less than 2 cm in diameter tumor may be more difficult due to the risk of false negative diagnoses with contrast imaging technique (50% of the cases) caused by immature arterial vascularization of the small nodules. Prognosis largely depends on the evolutionary stage at which HCC is detected, i.e. a size and number of HCC nodes, vascular invasiveness and degree of liver impairment. The multinodular pattern of HCC, representing one third of all early cancers, heralds poor prognosis, especially for patients not fitting the Milan criteria for liver transplantation. The best prognosis is for a single, less than 5 cm node in compensated cirrhosis without vascular invasion, since this tumor is amenable to both liver transplantation and hepatic resection which may confer long-term survival. Better survivals of cirrhotic patients with a recently identified tumors reflect the application of accurate criteria for tumor staging and stringent criteria for curative treatments. However, ageing of the patients, deterioration of liver function during surveillance, occurrence of multinodular tumors and limited access to liver transplantation may hamper surveillance programs effectiveness.*

KEY WORDS: Cirrhosis, Hepatocellular carcinoma, Surveillance.

## Introduction

Hepatocellular carcinoma (HCC) is a major health problem, worldwide. Approximately 600,000 new cases have been calculated to have occurred in the 2000 and, currently, HCC is the prime cause of death in patients with compensated cirrhosis[1,2]. Since HCC is a difficult to treat cancer, as suggested by the overlap between incidence rates and mortality rates, the only therapeutic hope is diagnosis of the tumor at an early stage, when potentially curative treatments can be applied[,2]. Following the identification of chronic liver diseases as relevant risk factors for this tumor, surveillance campaigns aimed at early detection of HCC are possible and thought to be the only practical approach for improving treatment of HCC[2]. By converse, surveillance cannot serve the few patients (<5% of all cases) with a HCC that do not develop on the background of chronic liver disease[3]. Most of these patients present late and have poor chances of cure. Our understanding of the natural history of HCC is of great help for appropriate selection of treatment and it is often hampered by the clinical heterogeneity of the tumor[4-7]. Currently, one-third of all patients referred to a third level hospital present with an early detected HCC, compared to 15 years ago when most patients with a HCC were diagnosed having advanced disease[8].

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## Early hepatocellular carcinoma

The concept of early cancer has been evolving during

Table I – *Diagnostic performance of ultrasound (US) as a screening test for HCC.*

| Outcome | Target population | |
| --- | --- | --- |
| | HBV carriers[17] | Cirrhosis[18] |
| Sensitivity | 79% | 58% |
| Specificity | 94% | 94% |
| Positive predictive value | 15% | 69% |
| Negative predictive value | 98% | 91 |

Table II – *Criteria applied for confirming HCC in patients with a node detected by ultrasound during the Barcelona Conference, 2005*[16]

• Histological criteria
• Non - invasive criteria (restricted to cirrhotic patients)
- Lesion has nodular configuration
- Lesion is at least 1 cm in longest diameter*
- Lesion shows arterial hypervascularization:
- lesions is detected as hyper-enhanced nodule in the arterial phase by two imaging techniques** OR
- lesion is detected as hyper-enhanced nodule in the arterial phase and as hypo-enhanced nodule in the portal venous or delayed phase by one imaging technique**

\* Apply to lesions emerged during US surveillance. For lesions detected at first imaging examination, lesion diameter should be at least 2 cm to allow non-invasive diagnosis of HCC.
\*\* Imaging techniques includes: contrast-enhanced US, contrast-enhanced spiral CT, and gadolinium-enhanced MR1.

the last decades thanks to the implementation of surveillance programs, worldwide. Surveillance has lead to increasing number of early detected cancers in the form of small nodules that first appear as well-differentiated tumors and proliferate along with gradual dedifferentiation, in a multicentric distribution or from dysplastic nodules[9,10]. In 1975, an early diagnosis of cancer was a 5 cm tumor developing in patients with compensated cirrhosis, in virtue of the excellent figures of survival obtained with hepatic resection as compared to patients with larger tumors[11]. In 1996, the concept of early HCC expanded to involve equal or less than 3 nodes of tumor each equal or less than 3 cm in diameter (Milan criteria), who survived following liver transplantation[12]. Lately, surgeons in Tokyo identified important clinical differences between 1 to 2 cm in size tumors, that may present with a fibrous capsule and/or fibrous septa, in contrast with other indistinctly nodular type cancers, that were detected as hypoechoic or hyperechoic nodules on ultrasound (US) examination[13]. Tumors with "indistinctly nodular pattern" have been considered as "carcinoma in situ" of the liver due to the absence of invasion into the portal vein branches and intrahepatic metastases[14] and may be differentiated from high grade dysplastic nodules because they cause stromal invasion[7]. From a clin-

ical point of view, indistinct tumor are difficult to treat since they almost invariably escape detection on contrast imaging in contrast with "distinctly nodular type" tumors which almost invariably show arterial hypervascularity on contrast imaging. In general, a combination of lack of fibrosis capsule and reduced number of unpaired arteries per square millimeter accounts for many false negative diagnosis of < 1.5 cm HCCs with contrast imaging[7].

## Surveillance

Screening is the application of diagnostic tests in patients at risk for HCC who are not suspected to carry a HCC[15] and surveillance is repeated application of screening tests, involving a process in which screening tests and recall procedures have been standardized[7]. In principle, screening for HCC is considered worth because HCC is a relevant cause of cancer-related death world-wide and early detection is the only practical approach to improve treatment outcomes[2]. Screening programs for HCC have been facilitated since the target population is readably identifiable (patients with cirrhosis, carriers of hepatitis B), the test adopted (abdominal ultrasound – US) has low morbidity and high diagnostic accuracy, and is acceptable to the population. During the EASL Monothematic Conference in Barcelona, 2005, recall procedures have been refined to identify HCC at early stages, when the tumor can be curable[16].
Abdominal US is the method of choice for both screening and surveillance. In both hepatitis B carriers and patients with compensated cirrhosis the sensitivity, specificity, positive and negative predictive values of US appear adequate (Table I) [17,18]. Six months are the ideal interval of screening with US since most cases of HCC double their volume in 6-month time[16]. The serum assay alfafetoprotein (AFP) is no longer considered for screening and surveillance, due to the high rates of false positive and false negative results in patients with chronic liver disease. Though a value of 20 ng/ml provides the optimal balance between sensitivity and specificity, however, at this level the sensitivity is only 60% while higher cut-off of 200 ng would increase specifity at the expenses of sensitivity (22%)[7]. AFP may still have an ancillary role in the few patients with a difficult to diagnose HCC, like tumors that do not appear at US as an expanding node, but silently infiltrate the liver[2]. These tumors, that can be visualized by spiral CT or MR do not conform, however, with the diagnosis of early diagnosis, since they are not amenable to radical therapies. An abnormal screening test needs to be confirmed by either an echo-guided liver biopsy or imaging-studies (Table II). Liver biopsy is indicated in patients with greater than 1 cm nodes who have no contraindications to invasive procedures and are candidate to curative surgery. The diagnostic accuracy of the procedure large-

ly depends on the size and location of the tumor which is approximately 70% for nodes between 1 and 2 cm in size[19]. Overall, the biopsy procedure is associated with a negligible risk of morbidity, mortality, and risk of seeding[20]. Diagnosis by imaging applies only to patients with cirrhosis, whose liver is mainly supplied by portal venous blood compared to HCC which is nourished by arteries. Lesions of at least 1 cm identified during surveillance and those of at least 2 cm detected at first imaging examination, need to be investigated with two coincident techniques among sonovue-US, spiral CT and MR. A single imaging technique is enough to diagnose HCCs showing wash-out of contrast medium following arterial hypervascularization. In anedoctal cases, diagnosis of HCC can be obtained combining an imaging technique with greater than 400 ng serum levels of AFP[2]. Smaller than 1 cm nodes are difficult to diagnose with imaging due to the low number of unpaired arteries, since these increase in parallel with the increasing size of the tumor[14]. Diagnosis can be solved in less than 50% of 1 cm nodes, these nodules, being the real diagnostic challenge. Close follow-up with US carried out at 3 month intervals (enhanced follow-up) is required to achieving a final diagnosis. It should be borne in mind, however, that imaging techniques may also generate false positive diagnoses in the presence of artero-venous shunts and macroregenerative nodules harbouring dysplastic liver cells[21].

According to the diagnostic algorithm proposed in Barcelona[16], cirrhotic patients showing no nodules during surveillance with US, will continue undergo surveillance at 6 months intervals (Figure). The efficacy of this diagnostic algorithm has recently been validated in Italy by Bolondi and coworkers[22] (Table III). In 84% of greater than 2 cm nodes and 44% of those between 1 and 2 cm the diagnosis was solved by imaging, whereas liver biopsy was diagnostically helpful in 16% of the former nodes and 27% of the latter ones. Twenty-nine percent of the cases were diagnosed as non-malignant nodes with both techniques.

## Tumor prognostication

The outcome of curative treatments is greatly influenced by tumor staging and adoption of the appropriate ther-

Table III – *Prospective validation of the diagnostic algorithm for HCC proposed in Barcelona 2000: the problem of hypovascular tumors[22].*

| Diagnosis | Modality of diagnosis | Node size | |
|---|---|---|---|
| | | 1-2 cm[a] | 2-3 cm[b] |
| HCC | Contrast US+CT | 18 (44%) | 26 (84%) |
| | Liver biopsy | 11 (27%) | 5 (16%) |
| Non malignant | Both | 12 (29%) | 0 |

Hypovascular with both techniques: a= 14 (34%); b=0

apy. Survival of HCC patients is predicted by criteria combining tumor characteristics, functional status and liver function. Tumor dedifferentiation and vascular invasion by tumor cells have constantly emerged as independent predictors of shortened survival in patients undergoing hepatic resection or transpantation for HCC. The size and number of HCC nodes are the best clinical surrogates predicting tumor dedifferentiation and vascular invasion[,2]. The Barcelona Clinic Liver Cancer (BCLC) staging classification[23] comprises 4 stages that select the best candidates for the best therapies available, i.e. from early tumor stage (Stage A) that includes asymptomatic patients with small tumors suitable for radical therapies to late tumor stage (Stage D) that includes patients with untreatable disease (Table IV). Approximately one third of all patients present with an early stage HCC which is fit for radical treatment. Following proper selection of candidates to resection, liver transplantation and percutaneous interstitial treatments, 5-yr survival rates ranged between 50% to 70% (), with evidence that therapies actively modified the natural course of the disease. Prognosis of HCC was assumed to be poor in patients not fitting for the above mentioned radical therapies. Patients with larger than 5 cm tumor or more than 3 nodes each less than 3 cm in size, with compensated liver disease lacking vascular invasion or extrahepatic spread of the tumor have an expected spontaneous survival of 50% of 3 yr (intermediate stage of BCLC). Similar patients with more deteriorated liver function and/or vascular invasion by the tumor have advanced tumor disease, with a dismal prognosis of less than 10% survival at 3 yr (stage C of BCLC). End-stage HCC includes terminal patients, including Child-Pugh C patients with spontaneous bac-

Table IV – *The Barcelona Clinic Liver Cancer Staging Classification of patients with hepatocellular carcinoma[23].*

| Staging | Performance status | Tumor stage | Child-Pugh |
|---|---|---|---|
| (A) Early | 0 | Single < 5 cm 3 nodes < 3 cm | A & B |
| (B) Intermediate | 0 | Large/multinodular | A & B |
| (C) Advanced | 1-2 | Vascular invasion extrahepatic spread | A & B |
| (D) End-stage | 3-4 | Any of the above | C |

Table V – *Cancer of the Liver Italian Program (CLIP) staging classification of hepatocellular carcinoma[8].*

| Score | Tumor morphology | Child-Pugh | AFP | Vascular invasion |
|---|---|---|---|---|
| 0 | Uninodular < 50% of the liver | A | < 400 mg/dl | No |
| 1 | Multinodular > 50% of the liver | B | > 400 Mg/dl | Yes |
| 2 | Massive | C | – | – |

Table VI – *A randomized controlled trial of screening for hepatocellular carcinoma (HCC) in individuals with hepatitis B markers or a history of chronic hepatitis[35].*

| Outcome of screening | Screening* | Controls | |
|---|---|---|---|
| Persons years | 38,444 | 41,077 | |
| No. HCC detected | 86 (224 x 10$^5$) | 67 (163 x 10$^5$) | RR: 1.57 (CI 0.99 – 1.89) |
| Small tumors detected | 39 | 0 | p< 0.009 |
| Treated with resection | 40 (46.5%) | 5 (7.8%) | p< 0.009 |
| Five-year survival | 46.4% | 0 | p< 0.001 |
| Deaths from HCC | 32 (83 x 10$^5$) | 54 (131 x 10$^5$) | RR: 0.43 (CI 0.41 – 0.98 |

* less than 60% adherence to surveillance.

terial peritonitis, whose survival does not exceed 6 months.

The Cancer of the Liver Italian Program (CLIP) system allocates points for four variables that affect prognosis including Child-Pugh stage, tumor morphologic features (single, multiple or massive tumor), serum AFP level and portal vein thrombosis (Table V)[8]. Although this scoring system has been partially validated and is easy to use, the CLIP score has suboptimal sensitivity for tumor invasiveness, since patients with score of 0 may have from 0 to 50% of their liver replaced by HCC. Since the score is definitively skewed toward more severely affected patients whose disease is not amenable to curative treatment, too many patients with a CLIP score of 0 will not meet the currently accepted criteria for surgery or locoregional ablation of the tumor that have been proven to be efficacious in patients in whom there is one tumor node of less than 5 cm in size[2]. In the recent years, other staging systems have been proposed including the Chinese University Prognostic Index[24], the modified TNM[25], a French score system[26] and a German score system[27]. Since staging scores developed thus far reflect differences in demographic features of the patients seen locally, expertise and treatment algorithms adopted in different centers, one wonders whether it is worth to attempt to reach consensus on a single model for staging HCC. From a clinical point of view, it appears mandatory that prognostication of liver cancer should always incorporate treatment-dependent variables[28]. In 2 studies, BCLC prove to be superior to CLIP and other scores in the prognostication of patients with a HCC[29,30].

## Natural history of the tumor

In most patients, HCC is first detected as a single, slowly growing node[2]. However, the tumor size when HCC is first detected does not predict the course of the disease in all cases, the median time of doubling volume for a small HCC ranging from 1 to 20 months[31]. While the tumor is a clinically indolent disease during the early phases of growth, advanced HCC may present with painful hepatomegaly and/or jaundice. In at least one third of all patients, HCC is first detected as a multinode disease. The multinodular pattern of the tumor is more common in patients with multiple etiological factors like viral hepatitis plus alcohol, than in those with a single etiologic factor[5]. Differential diagnosis between metastatic cancer and second primary tumors, is often difficult even matching radiological and histopathological findings on explanted or resected livers. Distinction between these two conditions, however, bears important clinical implications. Second primary tumors appear to be less aggressive than metastatic tumors[32], since they recur less frequently after ablation than the latter tumors. The wide differences in the growth pattern of HCC may have clinical implications, thereby influencing the choice and outcome of treatments. In general, slowly expanding tumors have a more favourable prognosis than fast growing, replacing type tumors[33]. Prognostication may be difficult in HCCs that have constant rates of growth during follow-up, while others either have a declining growth rate in the late phases of follow-up or, after an initial phase of resting, increase in volume exponential-

ly[31]. Due to this great diversity of the tumor growth patterns, the predictive power of the size of the tumor at diagnosis is not absolute and explains why prognostication in HCC patients can more reliably be obtained by combining tumor size with clinical data.

The presence of microscopic vessel invasion by the tumor, that is considered direct evidence of intrahepatic metastasis, bears important clinical implications, too. Vascular metastases, in fact contraindicate liver transplantation even though the risk of recurrence is not absolute. In patients treated with resection in Korea[34], up to 40% of less than 2 cm tumors had microscopic venous invasion, a funding that contrasts with the high post-transplantation cancer-free survival for patients meeting the Milan Criteria[12]. By converse, the risk of tumor recurrence for patients with macroscopic venous invasion, is virtually absolute. Not surprisingly, macroscopic venous invasion is a relevant predictor in the BCLC staging system.

## The role of treatment

Early detected HCCs have an excellent prognosis since they can be treated with potentially curative therapies. The five-year survival rates of accurately selected patients range from 50% for patients undergoing locoregional ablative therapies to 75% for those treated with liver transplantation or resection[2]. To date, there is only one randomized controlled study that assessed the impact of surveillance on patients at risk of HCC[35]. This was a population-based study carried-out in Shanghai residents with chronic viral hepatitis who underwent semi-annual screening with US+AFP. The study reported a 37% increase in survival for patients under active surveillance as compared to controls (Table VI). Since randomized controlled studies are no longer feasible in the clinical setting for ethical reasons: The impact of surveillance on outcome of HCC patients can be only assess retrospectively. The reanalysis of a cohort of 417 HCC-free patients with compensated cirrhosis who had been under prospective surveillance for 148 months, showed a fall in liver-related mortality rates in HCC patients identified between 1997 and 2001[6]. Mortality rates fell from 45% in the first quinquennium (1986-1991) to 37% in the second (1991-1996) and 10% in the third one (1997-2001; first vs second ns, first vs third  p=0.0009, second vs third p=0.018) in parallel with a reduction in yearly mortality of treated patients (34%, 28% and 5%: first vs second ns, second vs third p=0.036; first vs third p=0.0024). During the last quinquennium of surveillance, there was a shift of more patients from surgery towards the less aggressive locoregional ablative techniques, favoured by the application of stringent criteria for patients selection to hepatic resection and the limited availability of donated organs for treating HCC with liver transplantation. Also, fewer patients with a single small tumor were left untreated or missed radical treatments compared to previous periods (46% vs 38% vs 26%), and fewer patients treated with hepatic resection or locoregional ablative therapies died of causes unrelated to cancer (35%, 25%, 0%). The gain in survival of cirrhotic patients developing a HCC during the last 5 years likely was the consequence of improved management of the tumor and complications of cirrhosis.

## Causes of death

Among 112 patients with a prospectively identified HCC during surveillance, 82 patients died[6]. Fifty-two patients (63%) died of tumor progression, 7 (8%) of liver failure, 8 (10%) of gastrointestinal hemorrhage, 5(6%) of non liver conditions, 6 (7%) of unknown causes, and 2 (2%) of OLT-related complications. The fact that the vast majority of cirrhotic patients with a HCC died of intrahepatic tumor progression, justifies all efforts to local treatment of the tumor when liver transplantation is not feasible.

## Conclusions

Surveillance of patients with compensated cirrhosis aimed at early diagnosis provided important insights into the natural history of HCC. This is often a slowly growing tumor which is amenable to curative treatment when early detected in patients with preserved hepatic function. HCC arising in patients with liver impairment makes the prognosis dismal since these patients can only be saved by liver transplantation, i.e. a procedure that has several restrictions in terms of patient age, cancer progression and donated organ availability. The need for standardized recall policies during surveillance led to development of scoring systems, based on tumor and liver disease variables that predict patients survival. Despite widespread use of sensitive imaging, still limitations exist in the diagnosis of HCC in patients with liver nodules between 0.5 and 1.5 cm in diameter. In perspective, sophisticate approaches for prognostication based on genetic profiling of the tumor might improve selection to therapy of HCC patients.

### Riassunto

L'epatocarcinoma (HCC) è un tumore a lenta crescita, la cui storia naturale non è completamente nota. La diagnosi di un tumore piccolo, ben trattabile è resa possibile dai programmi di sorveglianza con ecografia dei pazienti a rischio. Un intervallo di sorveglianza di 6 mesi è considerato valido sotto l'aspetto di costo-efficacia, poichè permette l'identificazione di tumore <3 cm nella maggioranza dei pazienti. Nei tumori >3 cm che si

sviluppano in pazienti con cirrosi, la diagnosi è possibile con tecnica MR, CT o US + contrasto dimostrando ipervascolarizzazione nella fase arteriosa seguita da wash-out. La prognosi dipende dallo stadio evolutivo al momento della diagnosi, cioè dal numero, volume, invasità vascolare ed insufficienza epatocellulare. Tumori <5 cm in fegato compensato senza invasione vascolare hanno prognosi eccellente, poichè possono essere eradicati con tecnica chirurgica. L'invecchiamento dei pazienti a rischio ed il deterioramento clinico durante la sorveglianza, lo sviluppo di tumori multinodali ed il limitato accesso al trapianto di fegato, riducono l'efficacia dei programmi di sorveglianza per HCC.

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